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Maternal Asthma and Use of Antiasthmatic Drugs in Early Pregnancy and Congenital Malformations in the Offspring

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Abstract

Objectives: To investigate the risk of congenital malformations in infants born of women who had used antiasthmatic drugs in early pregnancy.

Methods: Data were obtained from the Swedish Medical Birth Register for 1996-2011. Information on drug use was based on midwife interviews towards the end of the first trimester. Presence of congenital malformations was ascertained from three national health registers. Risk estimates were made with Mantel-Haenszel odds ratios after adjustment for delivery year, maternal age, parity, smoking, and body mass index. Consideration was taken to concomitantly used drugs.

Results: Among more than 1.5 million women who gave birth, 2.9% reported the use of antiasthmatics. These women had characteristics which distinguished them from other women who gave birth and they more often than these used other drugs than antiasthmatics. These differences seemed to affect malformation risk only little. The risk for a major malformation was slightly but significantly increased (odds ratio=1.09, 95% confidence interval 1.03-1.12), specifically this was seen for cardiovascular defects, median cleft palate, and pyloric stenosis. There was no specific association with specific drugs or drug groups, the highest risk estimate was seen for women who used only one drug and notably a short-acting adrenergic or used three or more antiasthmatic drug groups.

4 Conclusion: The absolute risk for a congenital malformation in infants born of women using antiasthmatics is low and some evidence indicates that it is due to underlying asthma. A good control of asthma seems important and scare of teratogenicity of the common antiasthmatic drugs should not prevent adequate use.

Keywords: Adrenergic; Antiasthmatic; Asthma; Cardiovascular defect; Cleft palate; Congenital malformation; Glucocorticosteroid; Leukotriene receptor antagonist; Pyloric stenosis; Xanthine

Introduction

Numerous studies have been published on the effect of maternal asthma on pregnancy and pregnancy outcome, including the presence of congenital malformations. A summary of the early literature was published in 2007 [1]. Since then further studies have appeared and recent reviews are available [2,3]. A meta-analysis in the latter article found a weighted total odds ratio for a major malformation from four relatively large cohort studies of 1.18 (95% CI 1.00-1.36). Other studies used case-control approaches [4-6] and found statistically significant associations between maternal use of antiasthmatics and specific congenital malformations. As pointed out by many authors [2], a major problem in the interpretation of these results is the question of confounding by indication, that the underlying asthma and not the use of drugs caused the malformations.

The present study updates previous information from the Swedish Medical Birth Register on the association between maternal use of antiasthmatics and infant congenital malformations [7].

Material and Methods

The study was based on the Swedish Medical Birth Register which contains medical information on nearly all births in Sweden [8]. Since July 1, 1994, information on maternal drug use in early pregnancy was recorded from midwife interviews at the first prenatal care visit, usually in pregnancy weeks 10-12. Drug names were recorded in clear text and were later centrally transferred to ATC (Anatomical, Therapeutic, Chemical) codes. Women who had reported any antiasthmatic drug (ATC code R03) were identified and compared with women who did not report such drugs. The Medical Birth Register also gave information on putative confounders consisting of maternal characteristics and of concomitant use of other drugs than antiasthmatics. The maternal characteristics were maternal age (5 year classes, <20, 20-24 etc.), parity (1, 2, 3, ≥4, where parity 1 is the first baby born), maternal smoking (unknown, none, <10 cigarettes per day, ≥10 cigarettes per day), and BMI (unknown, <18.5, 18.5-24.9, 25-29, 30-34, ≥35) calculated from prepregnancy weight and height recorded at the midwife interview.

Outcomes were congenital malformations in the infants born. These were ascertained from three sources [9]: diagnoses in the Medical Birth Register given by the pediatrician who examined the newborn, the Birth Defect Register (previously called the Register of Congenital Malformations), and the inpatient discharge diagnoses in the Patient Register (previously Hospital Discharge Register). Information from the three registers was linked using the identification number which every person living in Sweden has.

In order to reduce variability in the ascertainment of congenital malformations, a subgroup called relatively severe malformations was formed where infants who only had one or more of the following malformations were excluded: preauricular tags, tongue tie, patent ductus in preterm infants, single umbilical artery, undescended testicle, hip (sub)luxation, and nevus. As cardiovascular defects were counted all cases with the exception of those with only a patent ductus at preterm birth or with single umbilical artery. In studies of specific malformations infants with chromosome anomalies were excluded.

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Risk estimates were made with the Mantel-Haenszel methodology as Odds Ratios (OR) with approximate 95% confidence intervals (95% CI) estimated with Miettinen's method. Adjustment was made for year of delivery, maternal age, parity, smoking in early pregnancy, and BMI. When the expected number of infants with the outcome under study was <10, a risk ratio was instead calculated as the observed/expected numbers with exact 95% CI based on Poisson distributions. Expected numbers were calculated with the adjustments mentioned above.

Ethics

The study was performed within the responsibilities of the National Board of Health and Welfare and therefore no ethical approval from outside ethical committees was needed.

Results

Among 1,552,342 women who gave birth and were registered in the Medical Birth Register in 1996-2011, 44 772 reported the use of antiasthmatics in early pregnancy (2.9%). Table 1 shows the number of women who reported the use of specific antiasthmatic drugs

Drug name	ATC code	Number of women	Number of infants
Adrenergics,		36682	37254
Short-acting			
epinephrine	R03AA01/R03CA01	104	104
ephedrine	R03CA02	31	31
salbutamol	R03AC02/R03CC02	8485	8597
terbutaline	R03AC03/R03CC03	27056	27362
fenoterol	R03AC04	36	37
Long-acting			
salmeterol	R03AC12	1806	1837
formoterol	R03AC13	1821	1850
bambuterol	R03CC12	15	15
Adrenergics+anticholinergics		41	41
salmeterol+ipratropium	R03AK04	41	41
Adrenergics+glucocorticoids		5291	5380
salmeterol +fluticasone	R03AK06	1730	1754
formoterol +budesonide	R03AK00/R03AK07	3571	3635
Inhaled gluco-corticoids		19258	19549
beclometazone	R03BA01	700	706
budesonide	R03BA02	17672	17901
fluticasone	R03BA00/R03BA05	949	962
mometazone	R03BA07	70	71
Anticholinergics		221	228
ipatropium	R03BB01	209	214
thiotropium	R03BB04	13	14
Antiallergics except corticosteroids		1681	1709
cromoglicic acid	R03BC01	1692	1709
Xanthines		209	214
choline theophyllinate	R03DA02	43	43
theophylline	R03DA04	163	168
amnophylline	R03DA05	5	5
Leukotriene receptor antagonists		506	512
montelukast	R03DC03	506	512
Antibodies		2	2
omalizumab	R03DX05	2	2
Unspecified		96	96

Table 1: Number of women reporting different specified antiasthmatics and number of exposed children.

Malformation	With drug	Total	OR/RR	95% CI
Any malformation	2206	70317	**1.07**	**1.03-1.12**
Rel. severe malformation	1544	45652	**1.09**	**1.03-1.15**
Chromosome anomalies	84	2932	1.01	0.81-1.26
Neural tube defect	24	734	1.13	0.75-1.70
Other CNS malformation	31	1131	0.92	0.64-1.32
Severe eye malformation	12	579	0.72	0.41-1.28
Severe ear malformation	4	280	0.45	0.12-1.15#
Cleft lip/palate	44	1704	0.87	0.64-1.57
Median cleft palate	42	1002	**1.45**	**1.06-1.98**
Cardiovascular defects	533	16145	**1.13**	**1.04-1.23**
Septum defects	144	4380	1.11	0.94-1.31
Esophageal atresia	14	445	1.12	0.66-1.90
Small gut atresia	13	392	1.22	0.70-2.13
Anal atresia	21	590	1.21	0.78-1.87
Pyloric stenosis	46	1101	**1.42**	**1.06-1.91**
Abdminal wall defect	10	413	0.84	0.44-1.60
Diaphragmatic hernia	9	368	0.79	0.41-1.52
Hyppospadias	120	4552	0.87	0.73-1.05
Severe renal malformation	26	882	1.00	0.68-1.48
Pes eqinovarus	74	2127	1.14	0.90-1.43
Poly/syndactyly	106	3084	1.21	0.99-1.47
Limb reduction defects	29	838	1.16	0.80-1.68
Craniostenosis	84	812	1.02	0.69-1.51
Rel. severe malformation except a cardiovascular defect	1090	34940	**1.07**	**1.01-1.14**

RR as observed/expected numbers with exact 95% CI.

Table 2: Congenital malformations after any antiasthmatic use. Odds ratio (OR) or risk ratio (RR) with 95% confidence interval (95% CI). Bold text shows statistical significance.

Some characteristics of the cohort are shown in Supplementary Table 1. The OR for each variable was adjusted for the other variables. The OR for use of antiasthmatics is increased in women below 25 and slightly low in women above 30. The OR is higher at parity 1 than at higher parities and there is a strong association with smoking and with high BMI.

Concomitant use of other drugs is shown in Supplementary Table 2. Adjustment was made for year of delivery, maternal age, parity, smoking, and BMI. These women used many other drug types more often than other women did. Some of these drugs may have a teratogenic activity of their own and may then confound the analysis. This could be true for drugs used at functional gastrointestinal disease, drugs for immunological bowel disease, antihypertensives, systemic glucocorticosteroids, thyroid hormones, and NSAIDs, either by drug effects or from underlying diseases.

Table 2 describes the presence of congenital malformations in infants born of women who used antiasthmatics. There were 45 652 exposed infants among 1,575,847 born. As can be seen from this Table, the ORs for any congenital malformation or for a relatively severe malformation were slightly increased and statistical significance was reached. Among specific congenital malformations, significantly increased ORs were seen for cardiovascular defects, other relatively severe malformations, median cleft palate, and pyloric stenosis. Some other conditions showed elevated ORs but none of them reached statistical significance.

Table 3 shows that exclusion of women who at the same time had used drugs with a possible teratogenic activity hardly affected

the OR for malformations and women who had reported the use of antiasthmatics and no other drugs had roughly the same risks as all women using antiasthmatics.

According to Table 4, significant effects on relatively severe malformations are seen after the use of one group of antiasthmatics alone and when three or more groups had been used while the OR estimates for use of two drug groups appeared to be lower. Table 4 also shows effects of different groups of antiasthmatics on the presence of relatively severe malformations. Even though only some reach statistical significance, there seems to be no clear-cut difference in effect between the groups – statistical significance is associated with large number of exposures. Also when individual antiasthmatics with at least 500 exposures were analyzed, ORs varied between 0.84 (95%CI 0.51-1.25, fluticasone) to 1.16 (95% CI 0.96-1.39, combination drug containing formoterol and budesonide) but the confidence intervals overlapped. When women who had used antiasthmatics together with systemic glucocorticosteroids were analyzed, the OR for a relatively severe malformation was 0.81 (95% CI 0.56-1.19).

In this Table comparisons are also made with different treatment combinations. In the first row under the sub-heading "Drug combinations", data on women who only used short-acting adrenergics are shown, in the second and third rows data on women who had used long-acting adrenergics or inhaled glucocorticosteroids for disease control. The estimated ORs for the latter groups are lower than for the former group but confidence intervals are wide so the differences may be random. For the fourth, rather small group, OR estimates are high but confidence intervals do not exclude 1.0

The OR for median cleft palate was 1.35 (95% CI 0.92-1.92) for short-acting adrenergics, 1.79 (95% CI 0.34-5.09, based on only 10 exposed cases) for long-acting adrenergics, and 1.65 (95% 1.11-2.44) for inhaled glucocorticosteroids. The use of combined long-acting adrenergic and inhaled glucocorticosteroids had an OR=1.83 (95% CI 0.84-3.47), based on only nine cases. None of the specific drug groups showed an increased OR for cleft lip/palate.

Among 512 infants exposed to montelukast, 17 had relatively severe malformations which are specified in Table 5.

Discussion

This study is based on a large material where drug exposure was identified by interviews in early pregnancy and congenital malformations from three national health registers. It has some weaknesses. Drug exposure occurred in early pregnancy and mainly during the first trimester but exact timing was not known. Some women may have used the drugs outside the period of organogenesis – this will result in a reduction of risk estimates. Another problem is that the study does not include cases where a congenital malformation was

			Relatively severe malformations		Cardiovascular Defects		
Group	Total number	With drug	OR	95% CI	With drug	OR	95% CI
All included	45642	1544	**1.09**	**1.03-1.15**	533	**1.13**	**1.04-1.23**
Excluding "teratogens"	42437	1441	**1.10**	**1.04-1.16**	491	**1.12**	**1.03-1.23**
Excluding all concomitant drugs	23556	794	**1.08**	**1.00-1.16**	270	1.11	0.98-1.25

Excluded "teratogens" are drugs used for functional gastrointestinal disease, drugs used for immunological bowel disease, antihypertensives, systemic glucocorticosteroids, thyroid hormones, and NSAIDs.

Table 3: Effect on relatively severe malformations or cardiovacular defects analyzed with respect to concomitant drug use. Odds ratio (OR) with 95% confidence interval (95% CI). Bold text marks statistical significance.

Antiasthmatic	Total number	Number malformed	OR/RR	95% CI	Number malformed	OR/RR	95% CI
Any antiasthmatic	45612	1544	**1.09**	**1.03-1.15**	533	**1.13**	**1.04-1.23**
Number of drug groups							
One	24144	842	**1.11**	**1.04-1.19**	284	**1.13**	**1.01-1.28**
Two	16749	534	1.03	0.94-1.12	187	1.08	0.93-1.25
Three or more	4145	166	**1.18**	**1.01-1.38**	61	1.27	0.98-1.63
Groups of drugs							
Short-acting adrenergics	35453	1219	**1.10**	**1.04-1.10**	433	**1.17**	**1.07-1.29**
Long-acting adrenergics	8947	287	1.08	0.96-1.22	102	1.12	0.92-1.36
Inhaled gluco-corticosteroids	24594	817	**1.08**	**1.01-1.16**	281	1.11	0.99-1.25
Anticholinergics	267	11	1.24	0.62-2.21#	3	-	-
Antiallergics	1709	57	1.01	0.77-1.32	18	1.01	0.63-1.61
Xanthines	214	8	1.04	0.45-7.06#	3	-	-
Leukotriene receptor antagonists	512	17	1.13	0.61-1.83	5	0.97	0.32-2.27#
Drug combinations							
Only short-acting adrenergics	20394	716	**1.13**	**1.04-1.21**	257	**1.22**	**1.07-1.38**
Long-acting adrenergic or glucocorticoids only	8467	270	1.07	0.95-1.21	86	1.01	0.81-1.25
Short-acting adrenergics+long-acting adrenergics or glucocorticoids	535	16078	1.07	0.98-1.67	192	1.15	0.99-1.32
Ditto+other antiasthmatics	24	598	1.24	0.82-1.86	10	1.52	0.73-2.71#

#RR as observed/expected numbers with exact 95% CI.

Table 4: Presence of relatively severe malformations or cardiovascular defects according to antiasthmatic used. Odds ratio (OR) or risk ratio (RR) with 95% confidence interval (95% CI). Bold text shows statistical significance.

Malformation	Number
ASD+VSD+PS+ CNS malformation	1
VSD	3
Unspecified cardiac defect	1
Larynx malformation	1
Tracheomalacia	1
Pyloric stenosis	1
Sponge kidney	1
Hydronephrosis	1
Pes equinovarus	1
Polydactyly hand	2
Syndactyly hand and foot	1
Upper limb malformation	1
Arthrogryposis	1
Wolf-Hirschorn syndrome	1

ASD=atrium septum defect, CNS=central nerovus system, PS=pulmonary valve stenosis, VSD=ventricular septum defect.

Table 5: Specification of relatively severe congenital malformations in infants exposed to montelukast.

identified prenatally and the fetus was aborted. Such cases are reported to the Birth Defect Register but without identification numbers which makes it impossible to identify maternal drug use. Finally, no direct information on the asthma status of the women existed.

A weak increased risk for a congenital malformation could be observed among infants whose mothers had reported the use of antiasthmatic drugs in early pregnancy. The effect was slightly stronger on cardiovascular defects than on other congenital malformations but the difference was not large.

The recorded total risk increase is small and hardly plays any role for the individual woman. If the risk estimate is true it means that the absolute risk increases with 10-15%, from 3% to 3.3-3.5%. Because asthma is a relatively common disease, such a risk increase will be of some significance in the population but even then it has no major impact. This estimate is much lower than those published from case-control studies (e.g., 4). An explanation may be that the present study was based on drug exposure ascertained prospectively in relation to pregnancy outcome while in the case-control studies ascertainment was retrospective with a risk of recall bias, to which is added a substantial non-response rate which may also result in skewed data. On the other hand, the present risk estimate for any major congenital malformation (1.09) agrees well with that obtained from a large cohort in UK (1.10) [10]. No statistically significant increased risk for major malformations was found in a Canadian register study of the impact of inhaled corticosteroids [11] but in a later and larger study [12] a significant risk increase (1.30, 95% CI 1.20-1.40) was found. In another paper studying the same cohort, the authors found an increased risk after high doses of corticosteroids (>1000 μg/day) but statistical significance was not reached [13]. In these studies there is a high rate of malformations in the unexposed cohort (7.5%) which indicates inclusion of minor anomalies, some of which may be the result of preterm delivery, e.g., undescended testicle and patent ductus arteriosus. An increased risk of preterm birth is seen with maternal asthma [1].

A specific association has been postulated between maternal use of antiasthmatic drugs, notably bronchodilators, and an increased risk for orofacial clefts [6], higher for cleft lip/palate than for isolated cleft palate. In the present study there were no signs of a risk increase for cleft lip/palate but there was one for median cleft palate but this was of similar strength for the various types of antiasthmatics and the lowest risk was actually found for short-acting adrenergics. The association between use of asthma medication and infant gastroschisis seen in one retrospective case-control study [14] was not verified in the present study – among 251 cases of gastroschisis only five had been exposed while seven were expected under a no-effect hypothesis.

The statistical association between maternal asthma and use of antiasthmatic drugs and the occurrence of congenital malformations can have many explanations. Maternal characteristics differ between these and other women. The effect of this is, however, small. The crude OR for a relatively severe malformation, adjusted only for year of delivery, is 1.13 (95% CI 1.11-1.15) and when adjusted also for age, parity, smoking and BMI it declines to 1.09 (95% CI 1.03-1.15). The corresponding figures for a cardiovascular defect is 1.15 (95% CI 1.05-1.25) and 1.13 (95% CI 1.04-1.23).

Another explanation is that women using antiasthmatic drugs use many other drugs more often than other women and if such concomitantly used drugs have an effect of their own on the malformation risk, this would confound the analysis. There was very little indication that this was true – the OR for a relatively severe malformation or for a cardiovascular defect was about the same when no other drugs had been used concomitantly or when women using drugs with a putative teratogenic risk were removed from the analysis.

A third explanation to the association is that asthma has an effect of its own, a confounding by indication. Such an effect can act in different ways, one possibility is that asthma exacerbations during early pregnancy could result in embryonic asphyxia and in this way cause malformations. Another possibility is a genetic link between the disease and some malformations. In the first situation, severity of the disease may decide the level of the malformation risk - a well-controlled asthma should have less or no effect. This may explain why the group with two antiasthmatics belonging to different groups seemed to have the lowest malformation risk. The one-drug group may be undertreated and the three or more drugs group may have asthma which is difficult to control needing a combination of many drugs.

Theoretically it would be ideal to be able to quantify the severity of the asthma in some way and add it as an explanatory variable [2]. There are clinical possibilities to do this, e.g., with spirometry or FEV_1 measurements [15]. A problem is that in order to demonstrate effects which are as weak as those we are discussing, large materials are needed. A power analysis (alfa=0.05, beta=0.80) shows that in order to demonstrate a 15% increased risk for any major malformation (supposing a 3% prevalence in the population) one would need to study about 11 900 women with asthma which in practice means the use of health registers where it is unlikely that data on clinical variables can be collected. The question whether the effect is due to drugs or to underlying disease most likely has to be answered in indirect ways. One way is to compare the effects of different drugs with the same indication. As seen in Table 4, no major differences are seen between different drug groups but the analysis is complicated by the fact that the drugs to some extent are used together and there are also differences between the drugs with respect to their clinical use.

Table 4 also shows that when different treatment situations are compared, no very strong difference appears but there is a suggestion that the OR is lower for women who are on prophylactic therapy with long-acting adrenergics and/or inhaled glucocorticosteroids. When other antiasthmatics had to be added (e.g., xanthines or leukotriene antagonists) the OR estimate increased but so did the confidence interval width. These observations suggest that the disease status in early pregnancy plays the major role for the slight malformation risk

increase and the consequence of this should be that as good control of the asthma as possible should be beneficial for the embryo and there is no reason to reduce or avoid therapy with adrenergics or glucocorticosteroids in early pregnancy for fear of teratogenicity.

In the arsenal of antiasthmatic drugs, some relatively recent additions are of special interest. One such drug group is leukotriene receptor antagonists, e.g., montelukast. Previous studies [16,17] were based on few exposures (96 and 180, with five and one infant with major malformations, respectively). The present material contained 512 exposed infants among which 17 had a relatively severe malformation. The risk estimate, 1.13 (95% CI 0.69-1.83) was of the same order of magnitude as for other antiasthmatics. So far, this drug seems not to carry a specific teratogenic risk but to exclude a weak such risk, a much larger material is needed. Another recent addition is the antibody omalizumab. Only two women reported the use of this drug, both with normal infants.

In conclusion, the present data show only a small risk increase for a congenital malformation in infants born of women using antiasthmatics and it seems likely that this risk is associated with poorly controlled asthma and not with drug use. Other obstetric and perinatal effects than congenital malformations may occur with maternal asthma. These have not been studied in the present investigation.

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